

REMARKS

I. Status Summary

Claims 1-42 are pending in the present application. Claims 1-42 stand rejected by the U.S. Patent and Trademark Office (hereinafter "the Patent Office").

Claim 11 has been amended. New claim 43 has been added. Support for the amendments and new claim can be found in the application as filed. No new matter has been added. Therefore, upon entry of Amendment A, claims 1-43 will be pending in the subject application.

Reconsideration of the application as amended and further in view of the remarks set forth hereinbelow is respectfully requested.

II. Response to the Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1-42 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants view as the invention. In particular, the Patent Office alleges that claims 1-42 are indefinite with respect to what constitutes the metes and bounds of a "nanoparticle." The Patent Office further alleges that while claim 11 recites a diameter, it is not clear if the nanoparticles are spherical or have some other shape or combination of shapes. See Official Action, page 2, point 3.

After careful consideration of the rejection and the Patent Office's comments, applicants respectfully traverse the rejection and offer the following remarks.

Initially, applicants respectfully submit that during examination, claims must be given the broadest reasonable interpretation consistent with the specification. See Manual of Patent Examining Procedure (hereinafter "MPEP") § 2173.05 citing *In re Morris*, 127, F.3d 1048, 1054, 44 USPQ2d 1023, 1207 (Fed. Cir. 1997); and *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). Further, applicants respectfully submit that claim terms are presumed to have the ordinary and customary meanings attributed to them by those of ordinary skill in the art. See MPEP § 2111.

Applicants respectfully submit that the term "nanoparticle" is an art-recognized term, and that, particularly in view of the specification, one of skill in the art would

understand the metes and bounds of the term “nanoparticle” as used in claims 1-42. Applicants respectfully submit that the specification as filed recites that the term “nanoparticle” means any structure comprising a nanoparticle,” and that typically, “but not necessarily, a nanoparticle is an approximately spherical metal atom-comprising entity.” See Instant Specification, page 28, lines 29-33, emphasis added. Moreover, the application as filed describes a variety of materials, size ranges, commercial sources, and fabrication methods relating to nanoparticles. See Instant Specification, Section II.E., “Nanoparticle Components”, page 28, line 7 to page 32, line 22.

Further, without acquiescing to the present rejection, applicants have, in an effort to expedite allowance of the claims, amended claim 11 to recite that the nanoparticle is approximately spherical. Support for this amendment can be found in the Instant Specification, page 28, line 32. Applicants note, however, that the term “diameter,” as used in a general sense, is not limited to spherical or circular objects, but can describe the distance between two sides of any object.

Accordingly, applicants submit that the present rejection of claims 1-42 under 35 U.S.C. § 112, second paragraph, as being indefinite is improper. Applicants respectfully request the withdrawal of the rejection of claims 1-42 under 35 U.S.C. § 112, second paragraph, and ask that claims 1-42 be allowed at this time.

III. Response to the Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-42 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Patent Office contends that the claims can be interpreted as allowing for the detection of any hybridization complex (i.e., a duplex or a triplex), wherein the capture probe may be a dendrimer comprising a multitude of double-stranded structures, wherein the method can encompass the differentiation of nucleic acids that have single nucleotide mismatches or may comprise nucleotide analogs, such as PNAs, which are recognized in the art for having higher binding affinity, and wherein the method can accurately and reproducibly detect the hybridization complexes when there is any concentration of target (including a single molecule). See Official Action, page 3,

point 6. The Patent Office further contends that of the five examples in the disclosure, only Example 5 is directed to the claimed invention, yet is silent with regard to how the method is conducted, how the results are interpreted, and how art-recognized issues relating to triplex formation, hair-pin structures, the sensitivity of thermal detection devices, thermal signature ranges, the affects of hybridization buffer components on light penetration, and the use of dendrimer probes may be accounted for. See Official Action, pages 3-4, point 7. Thus, the Patent Office contends that given the breadth of scope claimed, the limited guidance, the unpredictable nature of the art, and the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled. See Official Action, page 4, point 8.

After careful consideration of the rejection and the Patent Office's comments, applicants respectfully traverse the rejection and offer the following remarks.

Initially, applicants respectfully submit that the burden rests upon the Patent Office to establish a *prima facie* case of a failure to comply with 35 U.S.C. § 112, first paragraph. See *In re Marzocchi*, 58 C.C.P.A. 1069, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). As noted by the Patent Office, there are many factors to be considered when making the determination as to whether an application has met the requirements for enablement under 35 U.S.C. § 112, first paragraph, these factors including: (a) the breadth of the claims, (b) the nature of the invention, (c) the state of the prior art, (d) the level of ordinary skill in the art, (e) the level of predictability in the art, (f) the amount of direction provided by the inventor, (g) the existence of working examples, and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and MPEP § 2164.01(a).

Applicants respectfully submit that, in making its analysis of the *Wands* factors relating to the subject application, the Patent Office appears to have failed to take into account the full amount of guidance related to making and using the presently claimed subject matter provided throughout the specification and the high level of skill

in the relevant art, focusing instead to a large extent on the disclosure provided in the Examples alone.

Applicants respectfully submit that the specification as filed provides guidance concerning nucleic acid hybridization methods, for example, in Section II.G., "Sandwich Format Hybridization". See Instant Specification, page 35, line 26 to page 39, line 16. The specification references methods known in the art (see Instant Specification, page 37, lines 21-28), as well as specifically describing various aspects of nucleic acid hybridization. In particular, the specification describes methods for increasing hybridization stringency, such as through the use of high temperature and low ionic strength (see Instant Specification, page 37, line 33 to page 38, line 1), the use of formamide (see Instant Specification, page 39, lines 12-15), and the use of non-overlapping probes (see Instant Specification, pages 21, line 22 to page 22, line 2). The specification further describes how hybridization conditions can be varied based upon nucleic acid sequence length (see Instant Specification, page 38, lines 1-3; page 38, lines 22-24; and page 39, lines 1-4), and specifically describes that hybridization conditions may vary for modified sequences, such as PNAs, as would be understood by one of skill in the art. See Instant Specification, page 37, lines 27-28. Therefore, applicants respectfully submit that, after review of the specification as filed, one of skill in the art would understand methods that could be of use in forming hybridization complexes of a variety of nucleic acid sequences.

The application as filed also provides substantial information with regard to methods and apparatuses for photoexciting nanoparticles and detecting a change in temperature based upon the photoexcitation. See, for example, Instant Specification, Section II.H., "Detection of Hybridization Reaction", at page 39, line 18 to page 54, line 10. More particularly, the application specifically recites excitation wavelengths with regard to gold and silver. See Instant Specification, page 41, lines 19-24. The specification notes that for nanoparticles comprising metal oxides, the exciting light will generally be in the near-infrared range. See Instant Specification, page 41, lines 24-25. The specification also recites general factors to be taken into account when selecting a wavelength at which to irradiate nanoparticles, including the material

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comprising the nanoparticle, the shape of the nanoparticle, the size of the nanoparticle, and the thickness of the nanoparticle. See Instant Specification, page 41, lines 13-19. The specification describes that metal nanoshells are especially “tunable” and that the resonance of the optical absorption and the nonlinear optical properties of nanoshells can be systematically designed. See Instant Specification, page 32, lines 19-22.

With further regard to how the method is conducted, applicants note that several art-known apparatuses and methods for detecting temperature changes are suggested in the specification as filed, including, for example, calorimetry, infrared thermography, bolometers, thermopiles, pyroelectrics, micro cantilevers, and charge-coupled devices. See Instant Specification, page 41, line 32 to page 54, line 10.

With respect to the interpretation of results, applicants note that Example 4 describes how the amount of heat generated by irradiated nanoparticles is directly proportional to the concentration of nanoparticles attached to the surface. See Instant Specification, page 62, lines 2-6. Figure 15 illustrates this point, by showing the infrared thermogram of a glass slide attached to gold nanoparticles, the density of which increase from one end of the slide to the other. As the density of nanoparticles increase, the temperature increases. Similarly, Example 3 also describes data concerning the correlation of temperature increase with nanoparticle density. See Instant Specification, page 60, lines 23-26. That the number of nanoparticles will be proportional to the number of target nucleic acid molecules can be ascertained, for example, in Figure 17, which shows an embodiment of the presently claimed subject matter wherein the target nucleic acid can be prepared to include nucleotides modified by one ligand binding partner of a pair of ligand binding partners, allowing that target nucleic acid to bind to a given number of nanoparticles, which are attached to the other partner in the ligand binding pair. Thus, as described elsewhere in the specification, applicants submit that one of skill in the art would understand that a measured temperature, such as a temperature difference from background, can be correlated to the concentration of target nucleic acid in a sample (see Instant Specification, page 3, lines 30-32) because each hybridization complex

is associated with a target nucleic acid and one or more nanoparticles. For instance, applicants respectfully submit that, in view of the specification as filed, one of skill in the art would appreciate that a temperature difference caused by an unknown amount of a hybridization complex could be compared to the temperature difference caused by the presence of known amounts of hybridization complex, such as produced by a standardization curve resembling the data shown, for example, in Figure 16.

With regard to the Patent Office's allegations concerning "art-recognized issues," applicants respectfully submit that in view of the high level of skill the art of nucleic acid hybridization and thermal detection methods, and in view of the guidance provided by the specification, referenced hereinabove, one of skill in the art could predict, eliminate, or otherwise accommodate the use of hybridization buffer components affecting the penetration of light, triplex formation, or the presence of hair-pin structures within a probe or target. With regard to the Patent Office's allegations concerning the lack of guidance concerning the sensitivity of thermal detection devices, applicants respectfully submit that such information could be readily determined, either by data related to the thermal detection devices described in the specification, alluded to hereinabove, or through experimentation of a level regularly engaged in by those of skill in the art. Further, applicants note that Figure 16 suggests that the sensitivity of the infrared thermography method is such that the error in temperature measurements is 0.05°C. Applicants also note that the Examples provide guidance related to the range at which thermal signatures are to be read in the data presented describing ΔT levels found for various concentrations of nanoparticles and target sequence-associated nanoparticles. Finally, applicants note that the applicability of dendrimer probes to the presently disclosed subject matter could easily be assessed through experimentation, at a level which would not be considered undue in view of that regularly engaged in by one of ordinary skill in the art and in view of the present disclosure.

Accordingly, applicants respectfully submit that a *prima facie* case of non-enablement of claims 1-42 has not been made. Applicants respectfully request that

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the rejection of claims 1-42 under 35 U.S.C. § 112, first paragraph, be withdrawn, and further request that claims 1-42 be allowed at this time.

IV. New Claims

New claim 43 has been added. New claim 43 is directed to the method of claim 1, wherein the hybridization complex is present at a concentration of at least 10 fM. Support for claim 43 can be found in the specification as filed. In particular, support can be found in Example 5 (see Instant Specification, page 62, lines 16-17) and in Figure 16.

Applicants respectfully submit that new claim 43 is in condition for allowance and ask for a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

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DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any additional fees associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

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